REMARKS

The claims have been amended to place claim 5 in independent form having the features of claim 1, which has been canceled, incorporated therein and to correct informalities of claim dependence and antecedent basis. No new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention provides controlled release systems which take advantage of the property that the lower critical solution temperature (LCST) of the polymers making up the controlled release system increases when incubated in an aqueous medium, including aqueous surroundings in the body. The LCST of a polymer in an aqueous medium is the temperature below which the polymer is soluble and above which it is not. As explained in the specification, a drug, even a protein, can be loaded into the polymeric controlled release system by mixing with the polymer at a temperature below the LCST and then enmeshing the drug into particulate forms of the polymer by raising the temperature above the LCST. When this composition is administered, the drug is therefore not readily bioavailable.

However, because the polymer contains hydrolyzable groups, hydrolysis *in situ* changes the LCST. Thus, the particulate composition as administered has an LCST below body temperature, so the polymer containing the drug is insoluble. But upon incubation *in vivo*, the LCST is increased such that the particles are now in an environment where the temperature is below the new LCST. The polymer thus becomes soluble, and releases the drug.

Homopolymers of the monomer with the releasable moiety (in this case, the specified lactate) can be used or copolymers or interpolymers containing it can be used. Optionally, a hydrophilic polymer may also be included.

Priority

The Office asserts that applicants are not entitled to priority with respect to the parent application 10/048,732 (the '732). Applicants have verified on Public PAIR that this application is indeed identical to published PCT application WO 01/09198 (PCT/NL00/00542). Referring to this application, applicants are having difficulty seeing why priority is not accorded.

First, to take the last asserted deficiency first, the Office states that '732 does not contemplate controlled release systems, nor are such disclosed or taught in that application. However, page 4 at lines 27-29 specifically states, "The present invention provides a polymer that is suitable for use in a controlled release system. Consequently this polymer can be applied as a controlled release system having all the aforementioned advantages." Page 10, beginning at line 19, states that "the controlled release systems of the present invention can be prepared by the synthesis of a water soluble polymer." Page 10, line 32, begins "apart from application as a controlled release agent, the polymers of the present invention can be applied as release systems..."

Thus, it appears that there is explicit support for controlled release systems in '732 as published in the PCT application.

The Office states that the '732 only recognizes copolymers of N-(2-hydroxypropyl)methacrylamide lactate to be useful in drug delivery systems. It is stated that "every drug delivery system in '732 is based on micelles which are only formed from copolymers of the above lactate in a hydrophilic polymer." However, while copolymers are certainly preferred, it

is clear that homopolymers are recognized. For example, on page 5 at line 8, the specification says "when reference is made to a polymer in this description, also copolymers, terpolymers and other interpolymers are to be understood." The paragraph goes on to state that these have advantages but homopolymers are not disclaimed. In addition, a multiplicity of copolymers not involving, for example, PEG as a hydrophilic polymer is recited in claim 7 of the PCT publication and claim 9 claims a controlled release system comprising a temperature-sensitive polymer according to any of the preceding claims (including claim 7) and an active ingredient. In addition, Examples 9 and 10 of the PCT publication show degradation characteristics of homopolymers and copolymers which do not involve PEG or other hydrophilic units.

The Office appears to be attempting to limit the disclosure of the parent application to its preferred embodiments. As stated on page 7, "it is also possible to make the controlled release systems which can be obtained by the present invention in the form of polymeric micelles." That paragraph goes on to describe this possibility. However, the disclosure taken as a whole is by no means limited to this.

The Office goes on to say that the application does not teach how to make triblock, *e.g.* ABA, copolymers. It is asserted that the polymers in '732 are made from a PEG macroinitiator which is monofunctional, and thus terpolymers could not be obtained. However, page 9 of the specification, at lines 6, *et seq.*, specifically teaches how to make ABA block copolymers. The use of multifunctional initiators is specifically taught. It is certainly not the case that ABA copolymers are not envisioned.

For the reasons set forth above, applicants believe that priority is validly claimed.

Claim Objection

This is mooted by amendment.

The Rejection of Claims 5, 11 and 12 Under 35 U.S.C. § 112, First Paragraph / Enablement

Applicants assume that claims 6-10 are free of this rejection based on the fact that they require micelles and the use of a hydrophilic block.

First, it is irrelevant whether the prior art does or does not recognize the use in drug delivery of the invention polymers, that may not form micelles or that are not hydrogels. The specification itself describes how to do this. Specifically, paragraph 72 of the present application (which is also present in the parent on page 10, at lines 19-28) describes exactly how to do this. No mention is made of the need for a hydrophilic "block." The "water-soluble polymer" used in the release system must simply be soluble at a temperature below the LCST. It is possible, as indicated in the specification, simply to blend the polymers with the active ingredient to be released in order to form a matrix which is insoluble above the LCST.

As to the Wands factors, while the Office has stated the nature of the invention correctly, it is unclear what impact this has on the validity of the rejection. With regard to the state of the prior art, applicants are aware of no requirement that their invention be disclosed in the prior art.

With respect to working examples, while it is definitely helpful to have them, it is by no means required. In particular, the Office states on page 5 of the Office action that the applicants do not take account in the specification to working examples that N-(2-hydroxypropyl)methacrylamide lactate is not believed to form micelles or hydrogels unless it is part of a copolymer because it is so hydrophobic that homopolymers would not self-assemble in water. This fails to recognize the point

of the invention that these polymers are only hydrophobic above the LCST. Below the LCST, the polymer is hydrophilic.

With regard to the amount of experimentation necessary, the Office has adduced no evidence that any experimentation at all would be required in view of the directions provided in the specification, for example, in paragraph 72 thereof.

Thus, applicants believe that the rejection under 35 U.S.C. § 112, first paragraph, may be withdrawn.

The Rejection of Claims 5-12 Under 35 U.S.C. § 112, Second Paragraph

With regard to claim 5, the Office points out the LCST of a polymer is a property of a polymer that depends on the surrounding medium. This is already in claim 5 as it was, indeed, in claim 1. The LCST is referred to an aqueous medium. The amendment of the remaining claims to correct dependencies is responsive to the remainder of this basis for rejection.

The Rejection of Claims 5, 8, 9 and 12 as Anticipated by Cadée, *et al.*, of Record

For the record, Cadée, *et al.* Polymer (1999) 40:6877-6881 was published subsequent to the priority date herein. Verification of this attached as Exhibit A.

More importantly, Cadée does not undermine patentability even if it is citable prior art. Respectfully, applicants believe that Cadée (of which one of the inventors is senior author), does not disclose any polymers that include blocks formed by polymerization of N-(2-hydroxypropyl)methacrylamide lactate. Instead, Cadée discloses only polymers of dextran which are then derivatized with monomers of a different lactate. The lactate used in Cadée is shown on page 6878 in Figure 1. It is apparent that even these monomers are not those from which the polymers of the invention are formed as will be evident by comparing the structures in Cadée with

the structure in Figure 2 of the present application. But in any case, the hydrogel is formed not from the thermosenstive polymers of the present invention, but rather by the dextran. The lactate monomers of Cadée are simply coupled to it. Thus, Cadée does not describe homo- or inter-polymers of the required lactate, or even the monomer.

In addition, as to claim 12, there is no reason to attribute a homing function to the dextran. While paragraph 22 of the specification includes sugar moieties among the list of possible homing agents, it is clear form reading the paragraph as a whole that the sugar moieties must be such that they are directed to a particular target. This cannot be said of the dextran matrix of Cadée.

The Rejections Under 35 U.S.C. § 103

Claims 5-7 and 11 were rejected as assertedly obvious over Neradovic, *et al.*, *Macromolecules* (2001) 34:7589-7591. This is a paper describing the work of the present inventors published subsequent to the date from which priority is legitimately claimed. Accordingly, this basis for rejection may be withdrawn.

Claims 9 and 10 were rejected as assertedly unpatentable over Neradovic in view of Heller (US 5,939,453). As this rejection requires as primary reference the Neradovic document, which is not properly citable, this basis for rejection, also, may be withdrawn.

Conclusion

Applicants have demonstrated their entitlement to priority of the parent application which automatically overcomes the rejections based on Neradovic. Thus, claims 7, 10 and 11 are clearly free of the art. Claims 5, 8, 9 and 12 are not anticipated by Cadée because they do not disclose polymers formed from the required lactate.

Further, claims 5, 11 and 12 are enabled as the Office has offered no reason that the formation either of a hydrogel or the use of a hydrophilic polymer is required. For the reasons stated above, applicants believe claims 5-12 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 313632001120.

Respectfully submitted,

Dated: September 4, 2007

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Re: Publication date of an article published by Elsevier

Dear Ladies,

Further to our telephone conversation earlier today, I would kindly request you to let me know in writing in English:

1) the actual publication date; and
2) the date on which this publication was available on the internet
of the article "Synthesis, characterization of 2-(methacryloyloxy)ethyl-(di-) L-lactate and their application in dextran based hydrogels", published in Polymer 40 (1999) 6877-6881.

This letter is intended to be filed in the US Patent & Trademark Office.

Thank you so much for you kind cooperation.

Best regards,
VEREENIGDE
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EXHIBIT A

Wezel Y. van

From: AuthorSupportGlobal [AuthorSupport@elsevier.com]
Sent: dinsdag 6 december 2005 15:00
To: 'y.vanwezel@vereenigde.nl'
Subject: RE: zoals zojuist telefonisch besproken JPOL 4060

Dear Dr Wezel,

Thank you for your email.

The publication date of the printed issue was the 25 August 1999 and the online publication date was 16th August 1999.

If you require any further assistance please don't hesitate to contact us.

Yours sincerely,

Helen Sheridan

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